Public Comments on Proposed Selection of Bisphenol A for Preparation of Hazard Identification Materials

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Prior Evaluations of Bisphenol A

- Four comprehensive evaluations of bisphenol A have been conducted recently:
  - NTP Center for the Evaluation of Risks to Human Reproduction (CERHR, 2007)
  - European Food Safety Authority (EFSA, 2007)
  - Japanese National Institute of Advanced Science and Technology (2005)
  - European Union Risk Assessment (2003, 2008 update being finalized)
- Each evaluation focused on reproductive and developmental toxicity
  - These evaluations consistently show that bisphenol A is not a selective reproductive or developmental toxicant

CERHR Evaluation

- Most recent evaluation by CERHR panel of independent experts
  - Final panel report issued November 26, 2007
- Multiple comprehensive reproductive and developmental toxicity studies in laboratory animals were reviewed
  - Three multi-generation studies (2 in rats, 1 in mice)
  - NTP continuous breeding study in mice
  - NTP developmental toxicity studies in rats and mice

+ Robert Chapin (chair) – Pfizer, Inc.
+ Kim Boekelheide – Brown University
+ Simon Hayward – Vanderbilt University Medical Center
+ Barry McIntyre – Schering Plough Research Institute
+ Teresa Schnorr – NIOSH
+ John Vandenbergh – North Carolina State University
+ Jane Adams – University of Massachusetts, Boston
+ L. Earl Gray – US EPA
+ Peter Lees – Johns Hopkins University
+ Kenneth Portier – American Cancer Society
+ Sherry Selevan – US Public Health Service (retired)
+ Susan Woskie – University of Massachusetts, Lowell

Summary of CERHR Toxicity Conclusions

For reproductive and developmental toxicity, CERHR concluded:

- "Does *not* cause malformations or birth defects in rats or mice at levels up to the highest doses evaluated: 640 mg/kg/d (rats) and 1250 mg/kg/d (mice)."
- "Does *not* alter male or female fertility after gestational exposure up to doses of 450 mg/kg bw/d in the rat and 600 mg/kg bw/d in the mouse (highest dose levels evaluated)."
- "Does *not* permanently affect prostate weight at doses up to 475 mg/kg/d in adult rats or 600 mg/kg/d in mice."
- Did change the age of puberty in male or female rats at high doses (ca. 475 mg/kg/d).
  - Delays in preputial separation and vaginal opening, linked to body weight
  - These slight delays in pubertal landmarks did not affect reproductive outcome for any generation in a three-generation reproduction study in rats
- Based on the CERHR evaluation, bisphenol A has not been "clearly shown through scientifically valid testing according to generally accepted principles" to cause reproductive toxicity.

Summary of CERHR Concern Conclusions

- CERHR has five categories of concern expressed relative to current estimates of general population exposure levels:
  - Serious concern
  - Concern
  - Some concern
  - Minimal concern
  - Negligible concern
- Highest concern level for all endpoints was minimal or negligible, except “some concern” for neural and behavioral effects
  - Small number of small-scale animal studies “suggest” neurobehavioral effects
  - Unclear if these observations should be considered adverse
  - No definitive data available; additional research recommended

CERHR Evaluation Process is Sound

- CERHR evaluation process is scientifically rigorous and procedurally sound
  - Highly qualified scientific experts
  - Complies with Federal Advisory Committee Act guidelines to avoid conflict of interest among panel members
  - Open and transparent evaluation process with public participation
  - Final NTP report represents official view
- Process used for “Chapel Hill” statement on bisphenol A did not follow CERHR procedural guidelines
  - Closed process, conflict of interest not controlled
  - Not an official NIEHS activity or view

No Suitable Epidemiological Studies Exist

- CERHR panel concluded five available human studies are of limited utility for human health evaluation
  - Many limitations in design and analysis including:
    + Small size
    + Confounders and effect modifiers not effectively managed or controlled
    + Significantly different time-frames fro biological sampling (for exposure analysis) and occurrence/development of health effect
    + Analytical method unsuitable for measurement of bisphenol A
- These studies do not meet the Proposition 65 technical criteria for reproductive toxicity based on evidence in humans
  - Better characterized as exposure studies with descriptive cross-sectional components rather than analytic or epidemiological studies
- Bisphenol A should have failed the epidemiologic data screen for prioritization

Pharmacokinetics Predict Low Toxicity

- Bisphenol A has low bioavailability
  - Extensive presystemic clearance by intestinal and hepatic first-pass metabolism to conjugates
  - Conjugated metabolites (glucuronide, sulfate) do not bind to estrogen receptor; do not exhibit estrogenic activity in *in vitro* estrogen assays
- Human pharmacokinetics differ from rodents
  - Conjugates eliminated exclusively in human urine; half-life ~4 hours
  - No enterohepatic recirculation in humans
- Metabolism and pharmacokinetic properties of bisphenol A predict low toxicity for oral administration
  - Consistent with low toxicity observed in comprehensive and robust animal studies

Human Exposure is Very Low

- Urine biomonitoring is best means to directly measure human exposure to bisphenol A
  - Conjugated metabolites rapidly and completely eliminated into urine
- CDC urine biomonitoring data (NHANES 2003-2004) indicates typical human exposure is approximately 0.05 µg/kg-day
  - Study included >2500 participants, ages 6-85
  - Results are representative of US population
  - Consistent with urine biomonitoring results from other geographies
- Low human exposure consistent with bisphenol A use patterns
  - Limited potential exposure from use of consumer products
  - No consumer products contain more than trace impurity levels
- Tolerable Daily Intake of 50 µg/kg-day set by EFSA in 2007
  - Typical human exposure ~1,000 times lower than TDI

Conclusions

- Bisphenol A should not be considered a priority for review by DARTIC and OEHHA
  - Recent comprehensive reviews indicate that bisphenol A has not been "clearly shown through scientifically valid testing according to generally accepted principles" to cause reproductive toxicity
- Bisphenol A does not meet the Proposition 65 technical criteria for a recommendation as known to the State to cause reproductive toxicity
  - No suitable epidemiological studies exist
  - Multiple comprehensive animal studies consistently show that bisphenol A is not a selective reproductive or developmental toxicant
- Review of bisphenol A by DARTIC and OEHHA would consume considerable time and effort and likely duplicate the work of other highly qualified bodies